08/259,321

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/259,321	06/10/94	REZAIE	

EXAMINER

HM21/0831

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ART UNIT	PAPER NUMBER
1642	23

DATE MAILED: 08/31/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/18/98

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☒ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

PTOL-326 (Rev. 9/95)

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

1. Since this application is eligible for the transitional procedure of 37 CAR 1.129(a), and the fee set forth in 37 CAR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CAR 1.129(a).

2. Claims 1, 3, 7, 14 and 17 have been amended.
Claims 1-3, 5, 7-8, 14-15 and 17-21 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 2 and 15 are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Both claims recite two amino acid sequences (the third and fourth sequences of the Markush Group) that are not set forth in the "Sequence Listing." The applicant is advised to amend the claims to refer to these two amino acid sequences in text only, ""amino acids 20-139 of SEQ ID NO:10 and amino acids 23-129 of SEQ ID NO:12," deleting the recitation of the amino acid sequence themselves. Alternatively, the applicant can provide a replacement Sequence Listing that includes these two amino acid sequences.

5. This application contains two amino acid sequence disclosures (in claims 2 and 15, see above paragraph) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, as these two amino acid sequences are not included electronic and paper sequence listings, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. APPLICANT IS GIVEN THE RESPONSE PERIOD OF THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE

SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

6. The rejection of claims 1-3, 5, 7-8, 14-15, 17-21 under 35 U.S.C. § 112, first paragraph, as failing to provide complete evidence either that the claimed the hybridoma cell line ATCC No. HB 9892 is known and readily available to the public or complete evidence of the deposit of the biological materials is withdrawn. This rejection is withdrawn in view of the disclosure in the specification of the complete nucleotide and amino acid sequences of both the heavy and light chains of the monoclonal antibody secreted by ATCC NO. HB 9892 (SEQ ID NO's 9-12).

7. Claims 1-3, 5, 7-8, 14-15 and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations "humanized" in claims 1 and 15 and the recitation "humanized by the inclusion of a human constant domain or framework regions of the variable domain" in claim 2 are vague and indefinite. A humanized antibody is art accepted to be an antibody the possess the CDR (hypervariable regions) from the murine parent antibody. All other residues, both constant region and variable framework regions, are of human origin. Thus, it is unclear how the antibody of claim 2 can be humanized by either the inclusion of human constant region residues or by the inclusion of human variable region framework domains. Given that the humanized antibody of claim 1 is further limited by the specific humanization limitations set forth in claim 2, the broader nature of the "humanized" in claim 1 is unclear.

8. The rejection of claims 1-2, 5, 7-8, 14-15 and 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No.

5,202,253 is withdrawn in view of the amendment of the claims to include the limitation "humanized."

9. The rejection of claims 1-2, 5, 7-8 and 20 under 35 U.S.C. § 102(b) and (e) as being anticipated by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638 is withdrawn in view of the amendments to the claims to include the limitation "humanized."

10. The rejection of claims 1-2, 5, 7-8 and 20 under 35 U.S.C. § 102(b) as being anticipated by D'Angelo et al. (J. Clin. Invest. 77) or Stearns et al. (J. Biol. Chem. 263) is withdrawn in view of amendment to the claims to include the limitation "humanized."

11. The rejection of claims 1-3, 5, 7-8, 14-15 and 17-21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,202,253 in view of Morrison or Queen is maintained. Please see the arguments below.

12. As the parent application, 7/982,832 does not provide support for "humanized antibodies" or the synthesis of antibodies in insect cells, for the application of the art, priority to the instant filing date only (06/10/94) is extended to claims drawn to humanized antibodies and antibodies synthesized in insect cells.

13. Claims 1-3, 5, 7-8, 1415 and 17-21 under 35 U.S.C. § 103 as being unpatentable over any of U.S. Patent No. 5,202,253, U.S. Patent No. 5,147,638, D'Angelo et al. (J. Clin. Invest. 77) or Stearns et al. (J. Biol. Chem. 263) in view of view of Morrison, Queen (WO 90/07861) or Queen (U.S. Patent 5,530, 101, 6/25/96, filed 12/19/90).

The teachings and motivations provided by the cited references have been covered at length in previous office actions. Briefly, each of U.S. Patent No. 5,202,253, U.S. Patent No. 5,147,638, D'Angelo and Stearns teach monoclonal antibody HPC-4 and the hybridoma cell line that secretes the HPC-4 antibody. These references do not teach the humanization of said

antibody or its synthesis in bacterial or insect cells. However, Morrison and the two Queen references teach the complete methodology for the cloning and sequencing cDNA from the hybridoma cell line that secretes a given murine monoclonal antibody the nucleotide sequences that encode the immunoglobulin heavy and light chains (For example, see Example 5 of the Queen '101 patent) and complete methodologies for the construction of a humanized antibody using the hypervariable sequences obtained from these nucleotide sequences.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the basic methodology taught by Queen in order to clone the genes encoding the HPC-4 monoclonal antibody from the hybridoma cell line ATCC No. HB 9892 taught by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638, D'Angelo and Stearns. In doing so one of ordinary skill in the art would have obtained antibodies having the structural characteristics of those claimed. One of ordinary skill in the art would have been motivated to produce recombinant antibodies having the variable region of HPC-4 in order to obtain the advantages discussed by Morrison, for example, on page 1207. One would have been motivated to produce chimeric antibodies or humanized antibodies comprising human antibody sequences in view of the art-recognized advantages of reduced immunogenicity in human hosts obtained by replacing rodent antibody sequences with human sequences as discussed by Morrison and Queen.

The applicant argues that the Stearns reference was overcome as prior art in the prosecution of the parent applications, '638 and '253 and thus is not eligible as art in the prosecution of the instant application. In the absence of the presentation of the previous arguments and evidence presented in these parent applications for consideration in the instant rejection, this argument is not found persuasive. Affidavits or declarations, such as those under 37 CAR 1.131 and 37 CAR 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the original affidavit or declaration filed in the parent application. The applicant is invited to submit such arguments or evidence for consideration by the examiner.

The applicant that each of the argues each of the '638 and '253 patents and the D'Angelo and Stearns references (which teach the hybridoma cell line that produces the HPC-4 murine monoclonal antibody but do not teach methods for the humanization of antibodies) and the Queen reference (which teaches methods for the humanization of antibodies but does not teach the HPC-4 antibody) separately, do not enable the claimed invention. This is not found persuasive. As stated in the previous office actions, it is the combined teachings of these references that teaches and enables the humanization of the HPC-4 monoclonal antibody.

The applicant argues that the murine monoclonal antibody HPC-4 has very unique binding characteristics and it would not be obvious to one of skill in the art that this unique binding specificity would be imparted to the cloned, recombinant antibody taught by the combined references. This is not found persuasive. All antibodies, whether murine or human, share a high degree of structural homology, in the constant regions and the framework regions of the variable regions. Unique binding specificities are imparted to the antibody by the amino acid sequences of the hypervariable regions. One of skill in the art would reasonably expect the hypervariable regions of the HPC-4 antibody, when transplanted to a human antibody framework, would maintain the HPC-4 binding specificity. The applicant makes reference to declarations submitted in the parent case. Absent the submission of these declarations into the record of the instant case, these arguments can not be further considered.

The applicant argues that the claimed antibody can not be made without being in possession of the nucleotide sequence of the heavy and light chain variable regions. While this is correct, the examiner does not agree with the argument that said nucleotide sequences are not obvious in view of the combined teachings of the references. The applicant argues that it is the examiner's position that the nucleotide sequence is obvious from the HPC-4 antibody protein itself. This is incorrect. The nucleotide sequence is obvious in view of teachings of the hybridoma cell line that secretes the HPC-4 antibody protein. Combining this hybridoma cell line with the methodologies for cloning and sequencing immunoglobulin variable region sequences taught in the Queen and Morrison references, the nucleotide sequence of the HPC-4 heavy and light chain variable regions is obvious to one of skill in the art. The level of skill in the art of the

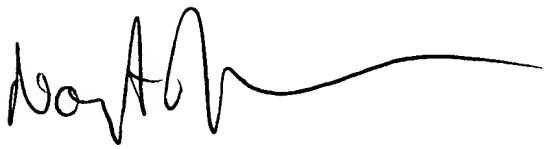
cloning the genes encoding antibodies was very high at the time of filing of the instant application, the applicant admits as much. The combined teachings make the nucleotide sequence obvious.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Johnson whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Nancy A. Johnson, Ph.D.
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August 26, 1998